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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 15

Application Number: 09/294, 663
Filing Date: 04/19/1999
Appellant(s): Granados et al

Thomas T. Aquilla
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed 04/26/2001.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is deficient because Appellants' specification on page 5, line 18 discloses IIM as "Invertebrate Intestinal Mucin", but not as "Insect Intestinal Mucin" as stated in page 2, line 1, under the Summary of the Invention.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 1, 6 and 9 stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

Dandekar et al. Plant Science, Vol. 96 (1994), page 151-162.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

(a) 35 USC 112, First Paragraph: Enablement

Claims 1, 6, and 9 on appeal stand rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a transformed plant comprising an isolated cDNA from *Trichoplusia ni* encoding the intestinal mucin (IIM) protein or SEQ ID NO: 3 or 4, and a method for producing and recovering *Trichoplusia ni* protein or peptide by transforming a host cell with an expression vector comprising SEQ ID NO:1 or 2 , does not reasonably provide an enablement for a transformed plant comprising a gene encoding an intestinal mucin protein of any invertebrate (IIM) protein, or a method of producing and recovering said protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims are broadly drawn to a transformed plant comprising any gene encoding any invertebrate intestinal mucin (IIM) protein from any invertebrate species, and a method for producing an IIM protein by transforming a host cell with a nucleotide sequence encoding a predetermined protein of any IIM. Invertebrates are a structurally and physiologically divergent category which includes insects, earthworms, and molluscs such as snails, clams, and lobsters. In contrast, the specification provides guidance only for a transformed plant expressing *Trichoplusia ni* cDNA or SEQ ID NO: 1 or 2 encoding IIM protein. The specification also disclosed 18 species of insects other than *T.ni* that comprise proteins that are recognized to some degree by antisera to *T.ni* IIM protein. The specification did *not* provide guidance for how to obtain other IIM *genes* from other insect species or other invertebrate species. No other DNA sequence from other insect species, and no protein or DNA sequence from non-insect invertebrate species, has been isolated or characterized. No specific guidance for obtaining the genes such as specific probes, hybridization stringency conditions, or gene sequence similarity has been provided.

Furthermore, no guidance was provided regarding the actual isolation of putative IIM proteins from the crude protein extracts which reacted with the anti- *T.ni*-IIM antibody . The first step in obtaining a gene encoding a protein is to purify the protein, sequence the protein, and then design nucleic acid hybridization probes which would encode part or all of the isolated , sequenced protein.

The proteins which the Appellants obtained from the other insect species were not purified IIM proteins. Most of the protein preparations were merely a *mixture* of solubilized insect midgut proteins, or a *mixture* of solubilized peritrophic membrane proteins, and even cruder *whole insect* extracts were used for mealybugs and whitefly (see page 32 of the specification, bottom two paragraphs). Thus the crude protein preparations cast doubt upon any data obtained by reacting antibodies thereto. Furthermore, the lack of purified protein for any non-*T.ni*-derived IIM protein would prohibit even the initial stages of gene isolation, as discussed above.

In addition, the majority of insect species which reacted with the anti- *T.ni*-IIM antibody were Lepidopterous species (butterflies or moths whose larval stage may be called "worms" in common, non-scientific nomenclature) closely related to the Lepidopterous *T.ni.* See Table 3 on page 31-32 of the specification. See also page 33, where only "strong" reaction with anti- *T.ni*-IIM antibody occurred with 5 species which were all Lepidopterous. Non-Lepidopterous species such as housefly, German cockroach or whitefly gave "moderate" reactivity at best; while other non-Lepidopterous species such as American cockroach, fungus gnat or mealybug gave no reactivity. Thus, even assuming that the data in the specification is probative of the isolation of IIM proteins from non-*Ti.ni* species, which it is not, the data is certainly not probative for obtaining isolated IIM proteins from a multitude of non-Lepidopterous insects, or from a multitude of *non-insect* invertebrates.

To claim transgenic plants expressing a multitude of IIM genes from a multitude of sources without any disclosure or guidance for how to obtain the genes is an invitation to

experiment requiring undue and excessive experimentation. *In re Wands, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)* lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and use the invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

The invention is a transgenic plant comprising a gene encoding an Invertebrate Intestinal Mucin (IIM). The IIM protein is characterized as peritrophic and chitin-binding membrane protein, localized in the mid-gut of invertebrate animals. The exact function of the IIM protein is not disclosed in the specification, however it can be inferred that the protein might provide resistance against insect attack upon its expression in transgenic plants (see, page 35, line 17 to page 36, line 21 of the specification). The specification discloses that the instant IIM was the first such protein to be identified from invertebrates (page 6, lines 5-6) . The specification discloses two cDNAs encoding two isoforms of IIM proteins from a single source, namely the insect species *Trichoplusia ni*. Appellants provided no guidance as to how one skilled in the art would be able to determine which gene(s) from a vast pool of genes, including undiscovered genes, would be the desired IIM genes or which would encode functional protein , which when expressed in plants induces insect resistance or any other agronomic traits , other than by random trial and error , thus requiring undue experimentation. To claim such genes without further

guidance as to how inoperable embodiments can be eliminated without undue experimentation is an invitation to experiment and does not fully enable the invention as commensurate in scope with the claims.

In addition, it is unpredictable whether the expression of insecticidal protein in transgenic plants will provide insect resistance. See, for example, Dandekar et al, (see, e.g., page 151, Abstract) who teach that expression of insecticidal proteins in transformed plants may fail to confer protection. Therefore, given the claim breadth, the state of prior art and level of one skilled in the art, the unpredictability inherent in the process and the lack of guidance as discussed above, the claimed invention could not be practiced by one skilled in the art without undue experimentation.

See Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ 2d 1016 at 1027, (Fed. Cir. 1991) where it is taught that the disclosure of a few gene sequences did not enable claims broadly drawn to any analog thereof.

(b) 35 USC, First Paragraph: Written Description

Claims 1, 6, and 9 on appeal stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims are broadly drawn to a transformed plant comprising a multitude of genes encoding a multitude of invertebrate intestinal mucin (IIM) proteins of a multitude of sequences from a

multitude of invertebrate sources, and a method for producing and recovering an IIM protein or peptide expressed in a host cell . The specification only discloses SEQ ID NO:1 or 2 encoding the *Trichoplusia ni* IIM protein or SEQ ID NO: 3 or 4. No other IIM genes have been isolated, characterized or described. No specific chemical or physical characteristics have been disclosed for these genes or their encoded proteins, other than those from *Trichoplusia ni*, and a review of literature does not indicate that such characteristics would be well known by a skilled artisan. Appellants did not provide a consensus sequence common to all members of the genus, a multitude of IIM genes encoding a multitude of IIM proteins, and because the genus is highly variant, SEQ ID NO: 1 or 2 alone is insufficient to describe the genus. The disclosure that the *T. ni* IIM protein contains high levels of threonine, alanine, and proline is not a unique property. Appellants merely disclose two protein isoform species from the single insect species *Trichoplusia ni* by complete structure, SEQ ID NO:1 or 2. The description of two species are not a representative sample of the genus and does not provide an adequate written description for the genus, a gene encoding an IIM protein.

Therefore, given Appellants' failure to provide specific sequence identification or any other property that show Appellants were in possession of the invention, a person skilled in the art would **NOT** recognize that Appellants were in possession of the invention at the time the application was filed. See *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ 2d 1016 at 1021 and 1027, (Fed. Cir. 1991) at page 1021, where it is taught that a gene is not reduced to practice until the inventor can define it by "its physical or chemical properties" (e.g a DNA

sequence). See *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), which teaches that the disclosure of a process for obtaining cDNA from a particular organism and the description of the encoded protein fail to provide an adequate written description of the actual of the actual cDNA from that organism which would encode the protein from that organism, despite the disclosure of a cDNA encoding that protein from another organism.

This Examiner's answer does not contain any new ground of rejection.

(11) Response to Argument.

(a) Enablement

Appellants insist , in pages 4-12 of the Brief, that the specification enables one of ordinary skill in the art for how to make and use the invention of claims 1, 6 and 9 . Appellants rely upon the following arguments to support their position:

- the Examiner's alleged failure to consider *Wands* factors as a whole when evaluating enablement (pages 9-11 of the Brief) ,

- the Examiner's alleged failure to determine enablement against the claimed subject matter (pages 8-9 of the Brief),

- assertions by the Appellant that the state of art is highly advanced , predictable and reliable for the transformation of any plant or expression of protein in any host cell (page 10, 2nd full paragraph of the Brief),

- assertions that the specification provides ample guidance in the identification and isolation of other IIM proteins from other species (paragraph bridging pages 10-11 of the Brief), and

- assertions that undue experimentation is not needed to make and use the invention (pages 11-12 of the Brief).

These arguments are not persuasive .

For considerations of enablement, although it is not required that the specification disclose what is well known in the art, the subject matter in the claims should be commensurate with the enabling disclosure. The instant claims are broader than the enabling disclosure as the claims encompass any gene from any invertebrate animal encoding any intestinal mucin protein. Appellants' disclosure of *Trichoplusia ni* IIM on April 19, 1999 , was the first to be isolated from any invertebrate. Apparently, IIM genes/proteins are not well known in the art. Therefore, the genes should be identified and characterized before their use for plant transformation. Since, the instant specification does not provide guidance for such identification or characterization, it is unclear how one skilled in the art is expected to obtain such genes.

Regarding *Wands* factors, the Examiner maintains that enablement was considered in view of *Wands* factors:

Guidance presented in the specification. No specific guidance has been presented for the isolation of the claimed multitude of invertebrate intestinal mucin (IIM) genes, such as as specific probes, hybridization stringency conditions, or gene sequence similarity. No guidance was presented even for the isolation of the encoded proteins, as stated above.

State of the prior art and level of skill in the art. Intestinal mucin or other membrane proteins/genes from invertebrates are not well known in the art, especially their identification and

expression pattern in host cells. Appellants disclose in page 6 of the specification, lines 5-6, that the *Trichoplusia ni* intestinal mucin was the first to be isolated from any invertebrate. While transformation of plants with heterologous genes is highly advanced , predictable and reliable, it is unclear how would one can ever carry out said method without having any guidance for how to obtain the multitude of claimed genes.

Breadth of the claims: Transgenic plants comprising *a gene* encoding *an invertebrate* intestinal mucin (IIM), production and recovery of *an IIM* protein in a host cell. The claims encompass a multitude of undiscovered genes whose expression in plants has yet to be investigated.

Working examples. No working examples for the transformation of plants or production of the protein in host cells are disclosed .

Unpredictability of the art. The unpredictability inherent in the instantly claimed invention lies not within the method of transforming a plant with a particular known gene to obtain a transformed plant, but with the *identification and obtention* of IIM gene(s) from a vast pool of invertebrate genes, including undiscovered genes, which would be the desired IIM genes or which would encode functional protein, and their *applicability in a method of their use* for conferring specific agronomic traits. In addition, it is unclear whether millions of insect species as well as millions of *non-insect* invertebrates would share common IIM proteins, since no evidence as such was provided.

Quantity of experimentation necessary. Given the lack of guidance for how to obtain any non-insect invertebrate IIM protein, any *purified* insect IIM protein, or any non-*Ti.ni* IIM gene encoding intestinal mucin, the quantity of experimentation required by one skilled in the art to produce transgenic plants comprising the gene or to produce and recover IIM protein in a host cell is undue and excessive.

Therefore, considering the *Wands* factors as discussed above, the claimed invention is not enabling as broadly claimed.

Regarding the enablement determination against the claimed subject matter, the Examiner maintains that issue of chitin-binding property, IIM antibody, and insecticidal activity are relevant to the claimed subject matter. First of all, Appellant should note that the claims do not stand in the vacuum, but are read in the light of the specification. The specification discloses these properties as unique and inherent properties. The properties of chitin-binding and insecticidal activity would be pertinent considerations when determining *how to use* the plant of claim 1 or the protein recovered from the process of claims 6 and 9, wherein considerations of *how to use* a claimed invention are pertinent to 35 USC 112, first paragraph. In addition, the recited properties of the protein would be required for the identification of IIM proteins in non-*Trichoplusia ni* invertebrates, wherein the identification of said proteins would be the first step in obtaining a multitude of isolated genes encoding them. These genes are required for the transgenic plant of claim 1 containing said genes, and are required for the method of using said genes of claims 6 and 9. Second, Appellants' arguments

that the specification expressly discloses the use of *Trichoplusia ni* antibody for the putative identification of IIM proteins from 18 other insect species (paragraph bridging pages 8-9 of the Brief) supports the Examiner's position.

(b) *Written Description*.

Appellants insist , on pages 12-19 of the Brief, that the disclosure conveys that the inventor had possession of the invention of claims 1, 6 and 9. Appellants rely upon the following arguments to support their position:

- assertions that Appellants' disclosure defines structural feature common to the claimed genus,
- Appellants' assertions the disclosure provides a representative sample of the claimed genus,
- Appellants' assertions that the instant Appeal discloses facts that distinguish it from *Regents,* and
- the alleged misapplication of *Amgen Inc. V. Chugai* to a Written Description requirement, rather than enablement issues.

These arguments are not persuasive because the claimed product and method employ structurally undescribed genes of which Appellants were not in possession at the time the application was filed.

Regarding 35 USC 112, first paragraph, it is not required that the specification describes what is already know in the art, however, the law requires the disclosure of a representative sample of species within the genus by either complete structure or by relevant characteristics other than structure. In the instant case, IIM or other mid-gut genes have not been disclosed in the prior art, and the disclosure of *Trichoplusia ni* cDNAs encoding IIM proteins does not provide adequate written description for the genus, a multitude of IIM genes from a multitude of

invertebrate sources encoding a multitude of IIM proteins used in the claimed methods and products.

Regarding the structural features common to all IIM genes/proteins, the Examiner maintains that the specification does not disclose structural features common to all genes from invertebrate intestinal mucin. Although the specification states that IIM protein contains high levels of threonine, serine, proline, glycine, and low aromatic amino acids, the specification does not state how these amino acids are structurally arranged, and it is unclear if the amino acid arrangement is common to all invertebrates. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed.

Regarding Appellants' assertion that the disclosure of 18 insect species in addition to *Trichoplusia ni* provides adequate written description for the claimed genus, the Examiner maintains that this assertion is incorrect. The specification describes only two isoforms of the *Trichoplusia ni* protein, and the corresponding genes, by complete structure. The specification also discloses that antiserum directed to *T.ni* IIM protein cross-reacted to some degree with crude preparations of mid-gut proteins from 18 other *insect* species (Table 3, pages 31-32 specification). The data are highly questionable, as discussed above, but certainly do not demonstrate the obtention of purified proteins from the subgenus of insects, and certainly do not characterize any protein or gene in terms of its sequence. Furthermore, no description was provided for *any* member of the larger subgenus, namely *non-insect* invertebrate IIM proteins or their corresponding genes. The subject claims present transformed host cells and methods that

employ undisclosed and discovered genes expected to be structurally different. Therefore, the disclosure does not provide an evidence of reduction to practice of the claimed invention.

Regarding the cited case law, the Examiner maintains that *Amgen Inc. V. Chugai Pharmaceutical* clearly presents written description issues in its teaching on page 1021, where it is taught that a gene is not reduced to practice until the inventor can *define* it by "its physical or chemical properties" (e.g., a DNA sequence). In *Amgen*, the inventors claimed a composition, an isolated DNA, which they did *not isolate and whose structure they did not know* . The " an IIM gene" transformed into the instantly claimed plant or used in the claimed method was NOT defined by *any* physical or chemical property, apparently yet to be discovered.

Regarding *Lilly,* the Examiner also maintains that *Lilly* is eminently applicable to the fact pattern of the instant Appeal . In *Lilly*, the Applicant claimed a genus of "any vertebrate cDNA encoding insulin" while disclosing the corresponding "rat cDNA". It was determined by the Federal Circuit that the rat cDNA *did not reasonably convey possession of the genus of every vertebrate cDNA,* even *if* the structures of the other vertebrate proteins were known . Similarly, the Appellants in the instant Appeal claim a transformed plant comprising *a gene* encoding *an IIM* protein, while disclosing only two cDNAs from a *single* insect species, *Trichoplusia ni*, encoding two isoforms of IIM protein. The fact that crude preparations of mid-gut proteins from 18 other insect species cross-reacted to varying degree with antiserum to *T.ni* IIM protein, did not shed any light on any feature of IIM proteins or genes common to all invertebrates, since the DNA sequences encoding said proteins are not disclosed, and since no purified proteins, much

less amino acid sequences, were disclosed. Therefore, the disclosure of two cDNAs from a single species, and/or the disclosure of impure, putative IIM proteins tested in 18 insect species do not provide adequate written description for the genes, as taught in *Lilly*. In addition, the claimed gene encompasses coding regions, introns, 5' and 3' regulatory elements, operons (if bacterial DNA) , and other untranslated regions which were not described in the instant specification. The application of *Lilly* to claims drawn to methods of using genes is specifically mandated by the Revised Written Description Guidelines, Federal Register Vol. 66, No. 4, issued Friday January 5, 2001 under "Notices". Therefore, the citation of the two cases by the Examiner is proper .

Therefore, given Appellants' failure to provide specific features for the claimed genes, the inventions in claims 1, 6 and 9 are not supported by an adequate written description.

CONCLUSION

For the reasons discussed above, it is believed that claims 1, 6 and 9 are not in compliance with 35 USC 112, first paragraph, regarding enablement and written description. Hence, the rejections should be maintained.

Respectfully Submitted,

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